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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,688	HERMANSON, GARY G.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *139,151 and 174* is/are pending in the application.

4a) Of the above claim(s) *140-150,152-173 and 175-214* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *139,151 and 174* is/are rejected.

7)☒ Claim(s) *174* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/31/2004;8/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

2. Applicants' amendment filed January 23, 2004 has been received and entered. Claims 1-135 have been cancelled. Claims 136-214 are pending.

Election/Restrictions

3. Applicant's election with traverse of the invention of group II (claims 174 and 214) filed January 30, 2006 is acknowledged. The traversal is on the grounds(s) that Examiner has not set forth convincing argument that the search and examination of group I along with elected group necessarily represents an undue burden for the examiner. Applicants' argument of examining plurality of polynucleotide composition with the elected group comprising a method of treating anthrax was found not persuasive. Furthermore, examination of method and composition group together would cause undue search burden, because examining a method claim for treating anthrax by polynucleotide is only one limitation and Examiner has to consider the method steps and perform searches. For example, a method for treating anthrax would be different from that of a composition comprising polynucleotide, which could be used in other

methods, and thus would require separate searches. These searches would be undue since method and factors affecting these distinct steps would have to be considered. Additionally, different inventions have different status in the art because they are drawn to different structure and functions. Applicant's also traverse the requirement of election of one Seq ID No. Applicant's argument of examining other sequences with elected Seq ID 4 was found not persuasive, as each of these sequences have distinct structure as stated in previous office action. However, fragments and variants of SEQ ID NO: 4 such as SEQ ID 2, 6 and 8 will be examined as long as they are dependent on elected claims. Therefore, claims 214 is withdrawn for examination purposes as it encompasses non-elected sequence ID NO.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 136-138, 140-150, 152-173 and175-214 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 30, 2006.

Claims 139, 151 and 174 are under consideration as drawn a method of treating or preventing anthrax infection in a vertebrate comprising administering to a vertebrate a composition comprising SEQ ID NO: 4.

5. Claims 139, 151 and 174 are under consideration.

Claim Objections

6. Claim 174 is objected to because of the following informalities: Claim 174 continues to depend in part to claim that is withdrawn and should be rewritten in independent form to recite elected invention. However, for purposes of compact prosecution, claim 174 will be treated as if dependent from claims 139 and 151. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 139, 151 and 174 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 174 is drawn to a method of a method to treat or prevent anthrax infection in a vertebrate comprising administering to a vertebrate in need thereof a composition comprising SEQ ID No 4 and a carrier recited in claims 139 and 151. It is emphasized

that claims 139 and 151 are drawn to a composition and carrier, however they are also analyzed for their intended use in method of treating or preventing anthrax infection.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: polynucleotide composition comprising any nucleic acid fragment that encodes a polypeptide at least 90% identical to amino acid

30 to 764 of SEQ ID NO: 4, the breadth of carrier and vectors that could be used to deliver DNA vaccine for the treatment or prevention by eliciting effective immune response to affect anthrax infection. It is noted that as instantly recited, claimed invention reads on broad genera of DNA vaccine by delivering codon optimized polynucleotide to elicit immune response, and delivery of DNA is generally not enabling in humans due to problems with, *inter alia*, targeting and expression of transgenes at effective level by any vector or other delivery vehicle to elicit therapeutic effective immune response. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in treating or preventing any form of anthrax infection by administering via any route and expressing plurality of codon optimized polynucleotide, (ii) the claimed method would have resulted in immune response sufficient to treat or prevent any form of anthrax. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in any subject. As will be shown below, these broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification provides a general description of anthrax infection and describes the role of toxins consisting of gene product protective antigen, lethal factor, and edema factor in the virulence of *Bacillus anthracia* infection (pp 1-2). The specification also describe the need for optimization of coding regions encoding polypeptides from pathogen codon frequencies preferred in a mammalian species resulting in enhanced expression in the cells of that mammalian species and concomitant increase in immunogenicity (pp 5). The invention is directed to enhance immune response of a vertebrate that require protection against anthrax by administering in vivo a polynucleotide comprising a codon optimized coding region encoding a component of *Bacillus anthracia* lethal toxin (pp 5-6). Pages 7-11 describe brief description of the drawing. Pages 11-67 of the specification provides a detailed description of the invention, preferred embodiments and provide definition of terms, codon optimization (pp 21-54), methods and administration of claimed compositions of the invention (pp 54). Rest of the specification provides specific examples of plasmid vectors, compositions and experimental details (pp 68-120).

As a first issue, the claim 139 embrace an isolated polynucleotide comprising a nucleic acid fragment which encodes a polynucleotide at least 90% identical to amino acid 30 to 764 of SEQ ID NO: 4, wherein said nucleic acid fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO: 4. The specification discloses a nucleic acid region for full length protective antigen (PA) (SEQ ID NO:4) and asserts other sequences that are human codon optimized coding region that encodes SEQ ID NO 4 (pp 71, para. 157). The specification also teaches PA

sequence encodes a 764 amino acid precursor protein that is processed by a signal peptidase upon secretion by the bacteria. However, specification fails to provide an enabling disclosure for the full scope of the claimed nucleic acid sequence. It is not apparent from the specification whether any sequence with 90% identity to SEQ ID 4 that is optimized for human codon would elicit effective immune response against *Bacillus anthracia* infection. The specification fails to provide adequate guidance how to make and use altered nucleic acid sequence for nucleic acid sequence ~90% identical to SEQ ID NO: 4, wherein fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO 4. Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) state, "interspecific difference of codon usage is one of the major obstacles for effective induction of specific immune responses against bacteria by DNA immunization". Nagata et al show that DNA immunization using the gene codon-optimized to mammals through the entire region is very effective (abstract). However, it is noted that Nagata et al suggest that translational efficiency of codon-substituted gene in mammalian cells does correlate but is not proportional to codon adaptation index (CAI) values of the genes in the mammals (Figure 2). Nagata et al conclude that only optimal codon usage elicit effective immune response (Figure 3 and pp 450, col. 2, last para). Thus, it is apparent that an artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would require undue experimentation to practice method as claimed because only optimal codon usage would have provided optimal immune response sufficient for the treatment of *Bacillus anthracia infection*.

While the specification provides a description of DNA vaccine for the protection against anthrax, the specification does not teach specific information required by the Artisan to reasonably predict that any form of anthrax infection can be treated or prevented by administering codon optimized DNA vaccine via any route such that it elicit an immune response that is effective for long enough for sustained period of time that would have beneficial effects in treating preventing or treating anthrax infection.

Applicant does not enable administering DNA vaccine via any route using any carrier to elicit an immune response. While progress has been made in recent years in development of DNA vaccine against viral as well as bacterial infection, however, desired immune response for sustained period continued to be unpredictable and inefficient in humans.

The state of the post filing art effectively summarized by the references of Galloway et al (Expert Opin Biol Ther. 2004, 4(10): 1661-7) describe progress made in DNA vaccine for the treatment and prevention against anthrax infection. Galloway state, " a number of factors may account for poor immunogenicity of plasmid DNA in non human primate and human. Of the prime importance is the issue of DNA uptake and antigen presentation" (pp 1665, col. 1, last para). It is disclosed that codon usage and cationic lipids improve the efficacy of the antigen presentation and resulting immune response. However, Galloway concludes, " the field of DNA vaccination remains largely an experimental and some what empirical science" (pp 1665, col. 2, para. 4, lines 1-4). They highlight some advantages of using DNA vaccine but also acknowledge the fact the no DNA vaccine is yet produced is not the research failure but

rather realization of complex role of immune system (pp 1665, col. 2, para. 4). The prior art of record on treating anthrax by recombinant anthrax vaccine was unpredictable as a number of question remain unanswered that require experiment that are not routine to determine whether the vaccine would be efficacious in any patient. For instance, Leppla et al (J Clin Invest. 2002,110(2): 141-4) while reviewing state of anthrax vaccine raise a number of questions. Leppla et al describe that limited clinical data and substantial animal experimentation indicate that only a critical level of serum anti-PA antibodies confer immunity to both cutaneous and inhalation anthrax. Leppla further describe a number of other uncertainties including what would be the optimal concentration of serum antibodies in humans that confers immunity to anthrax. Thus, a regimen of dose scheduling as disclosed from small animal and primate would not be efficacious to confer immunity in humans. In addition, the level of antibody required to protect individual from the effects of a anthrax infection is uncertain, since this would be dependent upon how the infection is acquired (bio-terrorist attack, natural, Zoonotic) and the number of spores inhaled. Similarly, the efficacy of this DNA vaccine would also be different depending upon source and route of anthrax infection (inhalation, cutaneous). The working example merely show immune response against spore challenge of 50LD $_{50}$- 250LD $_{50}$. It is not apparent whether it would confer protection against anthrax infection of 500- 5000 LD_{50}. Leppla et al also describe other source of anthrax exposure that could include aerosolized spores from an "anthrax bomb," resulting in spores in drinking water or food and other daily use material. It is described that these spores would not be totally inactivated by boiling and could pose a continual

threat. It is not apparent that a DNA vaccine as recited in this application would confer any protection to a long-term constant threat of anthrax infection. Leppla also questioned whether physicochemical and immunochemical assays could accurately predict the efficacy of a recombinant vaccine (pp 143, col. 2, para 2 bridging pp 144, col. 1, para. 1). The specification does not provide any specific guidance to overcome this art recognized unpredictability in dose, type and route of anthrax infection and levels of antibody optimal for protection or treatment in any subject.

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples describe the construction of an isolated polynucleotide comprising a human codon optimized PA, LF, fragments and variants thereof encoding full length *B. Anthracis* protective antigen (PA), LF and variant. The results show *in vitro* expression of human codon optimized coding regions encoding *B. Anthracis* PA, LF and fragments in a murine and human cell lines. The samples were assayed for by western blot and ELISA using anti PA, anti LF antibodies (pp 88-89). Examples 8 and discloses mouse, rabbit, non-human primate and human immunization by administering plasmid constructs intramuscularly and immunological assay to determine LF and PA antibody titer (pp 93-95). Examples 11-12 describe immunization of mice and rabbit using codon optimized *B. Anthracis* DNA vaccine in different cationic lipid formulations. The results show higher neutralizing antibody titer. The example also teaches immunization of rabbit using codon optimized intramuscular administration of *B. Anthracis* DNA vaccine

followed by aerosol administration of 50-250 LD_{50} equivalent of *B. Anthracis* (Ames strain) spores. The results show that all the codon optimized DNA vaccine formulations had comparable efficacy as compared to commercially available AVA vaccine. Examples 14-15 describe immunization of mice using formulation that is prepared by adding sterile plasmid DNA and sterile DMRIE: DOPE SUV liposome in a final molar ratio of 4:1 or 2:1 plasmid DNA to DMRIE and non human primate immunized by VR6292 formulation with Vaxfectin. The data shows enhanced anti PA IgG titer in different formulations (table 19-23). Example 16 shows long-term immune response in DNA immunized rabbit after anthrax spore challenge (pp 112, table 24).

Although instant application shows the potential role of codon optimized DNA vaccine against *B. Anthracis* infection, however, the specification does not provide any evidence that codon optimized polynucleotide could be delivered by any method using any route that would elicit a therapeutic effective level of sustained immune response that would confer immunity against infection in humans.

It is emphasized that the examples do not teach all the possible variant of SEQ ID 4 wherein nucleic acid variant is a variant of an optimized coding region for the polypeptide of SEQ ID NO 4. In addition, the specification also does not provide any specifics regarding power calculation that were used to demonstrate effectiveness of DNA vaccine and their role in enhancing immune response. The method of gene delivery and efficacy of DNA vaccine in a subject was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions in humans. It is noted that

the working examples describe mean genometic titer in 8-10 animal. The variability in neutralizing antibody data underscores the enhanced immune response seen with DNA vaccine with multiple formulations (Table 19-24). Brey et al (Ann N Y Acad Sci. 1997; 823:97-106) states, "studies involving animal models like those involving human subjects should use a sample size that ensures adequate power. It is not surprising that studies that use sample sizes as low as four to five animals per group would find discrepant results" (pp 103, summary). The specification does not provide adequate sample size that would be give appropriate power. In addition, the scope of invention as claimed encompasses administering the DNA vaccine using non-viral and viral vector via any or all route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.). It has been difficult to predict the efficacy and outcome of transduced therapeutic genes because factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. The transduction of target cells represent the first critical step in any gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. In addition, besides the limitations in gene transfer the problem to selectively target cell s in vivo is still one of the most difficult obstacles to overcome. For example, upon systemic administration the viral and non-viral particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. Besides intramuscular administration, the specification merely contemplates mucosal DNA vaccination by plurality of route without providing any specifics (pp 116, para. 249) or showing that

other routes of administration would result in generation of sustained immune response in the injected animals.

The specification also describes treating anthrax in any subject having any form of anthrax by administering any vector comprising lipid formulations. The specification contemplate using cationic lipids for delivering the DNA vaccine, however, The specification also describes treating anthrax in any subject having any form of anthrax by administering any vector comprising any lipid formulations. The specification contemplate using cationic lipids for delivering the DNA vaccine, however, prior art summarized by the references of Jones et al (Eur J Pharm Biopharm. 1999, 48(2): 101-111) and Perrie et al (Vaccine, 2001, 19(23-24): 3301-10) suggest that the physical stability, composition of liposomes and an appropriate surface charge (or zeta potential) contributes to optimal immune responses to the antigen encoded by the liposome (Jones et al pp 109, col. 1, last para and Perrie et al pp 3308, col. 2, para. 1).

It is apparent that each DNA vaccine will have its own structure. Thus, each DNA molecule depending on lipid composition would have different influence of zeta potential on the pharmacokinetics and bio distribution of the carried DNA vaccine. The specification does not provide any specific guidance on the influence of complexation of genus of DNA vaccine to plurality of cationic polymer to form polymeric micelles. The specification does not provide any specifics in terms of particle size and zeta potential of these micelles and dependence or independence lipid formulations while contemplating delivering plurality of molecules to genus of target site. In view of foregoing discussion, it is clear that the skilled artisan would require undue experimentation which is not

routine to practice claimed method to deliver plurality of compositions as contemplated by the instant claim particularly given the unpredictability of polymeric micelles and delivery of therapeutics using lipid formulations as whole and unpredictability expressed in the art.

The method disclosed in specification also contemplates using lipoplex-mediated delivery of DNA vaccine in the subject. Dass et al (Journal of Pharmacy and Pharmacology, 2002, 54, 593-601) describe various factors that influence lipoflex-mediated nucleic acid transfer in vivo that includes type of cationic lipid making up the vesicle, cationic to neutral lipid ratio, and type of neutral lipid in the vesicle (pp 594, col. 1, para 3). Dass et al conclude that in spite of cationic lipid-DNA complex being the efficient way to deliver nucleic acid into cultured cells. However, it is noted that Dass et al emphasize that their *in vivo* efficacy of lipoflex mediated nucleic acid delivery has shown varying degree of success, primarily due to toxicity associated with these formulations (pp 598, col. 1, last para). It is not apparent as how skilled artisan would carry over a method encompassing treating or preventing any subject infected with any form of anthrax infection by administering via any route a DNA vaccine comprising any formulations.

Furthermore, It is noted that, the specification does not teach whether disclosed DNA vaccine would be effective in treating or preventing all type of anthrax infection by administering codon optimized DNA vaccine using any carrier either via any or local route in any patients. The cited arts clearly indicate an unpredictable status of the DNA vaccine art pertaining to treatment of anthrax infection. Although, specific DNA vaccine,

codon optimization, and route of administration might be or may have been effective for treatment of specific viral or bacterial disease by providing enhance immune response.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of DNA vaccine such that it render any subject sufficiently to elicit a immune response for a sustained duration for the prevention or treatment of anthrax infection caused by any type or severity or route. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of DNA vaccine and *in vivo* delivery and treatment of anthrax in general by recombinant vaccine in vivo was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 174 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claims 174 uses a gene therapy composition for treating anthrax, but the claim does not set forth any steps involved in method/process, it is

unclear what method /process applicant is intending to encompass. The claim merely recites a gene therapy method without any active, positive step delineating how claimed method will actually be practiced.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 139, 151 and 174 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998).

Lee et al teach a method and composition for using the nontoxic protective antigen (PA) protein from *B. anthracis* in inducing an immune response that is protective against anthrax in subjects (abstract). It is noted that Lee et al disclose a SEQ ID NO: 6 (PA) that has 100% sequence similarity with claimed SEQ ID NO: 4 (see sequence search report). It further discloses that nucleic acid molecules could encode portions or fragments of the nucleotide sequences and variants of disclosed sequence (pp 2, para. 24 and 25). Lee et al emphasize that it would be routine for one skilled in the art to

generate the degenerate variants, for instance, to optimize codon expression for a particular host (pp 2, para. 21, col. 2, lines 1-5). Therefore, any codon alteration of the bacterial codon usage to human codon usage is inherent in the teaching of Lee. Furthermore, Lee et al also contemplate using pharmaceutical carrier to deliver disclosed nucleic acid composition for eliciting immune response in a subject (claim 20).

Accordingly, Lee et al anticipates claims 139, 151 and 174.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 139 and 151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998) or Katritch et al (US Patent publication no. 20030235818, dated 12/25/2003, effective filing date 4/17/2002) or Collier et al (US Patent publication no.

20020039588, dated 4/4/2002, effective filing date 5/4/2000) and Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51).

Lee et al teach a method and composition for using the nontoxic protective antigen (PA) protein from *B. anthracis* in inducing an immune response that is protective against anthrax in subjects (abstract). It is noted that Lee et al disclose a SEQ ID NO: 5, 6 (PA) that has at least 90% sequence similarity with claimed SEQ ID NO: 4 (see sequence search report). It further disclosed that nucleic acid molecules could encode portions or fragments of the nucleotide sequences and variants of disclosed sequence (pp 2, para. 24 and 25). Lee et al emphasize that it would be routine for one skilled in the art to generate the degenerate variants, for instance, to optimize codon expression for a particular host (pp 2, para. 21, col. 2, lines 1-5). In addition, Lee et al contemplate using pharmaceutical carrier to deliver disclosed nucleic acid composition for eliciting immune response in a subject. Since the disclosed nucleic acid sequence is from *B. anthracis*, the codon usage pattern is considered related with the translation efficiency of the gene in different organisms. Katritch et al and Collier et al also teach SEQ ID No: 30 and SEQ ID NO; 1 respectively that has at least 90% sequence similarity with claimed amino acid 30-764 of SEQ ID NO: 4 (see sequence search report). It is also noted that these compositions were directed towards enhancing immunity against *B. anthracis*. The prior art differs that it does not explicitly provide motivation for codon optimization to enhance immune response in a subject using the *Homo sapiens* codon frequency table.

At the time of invention, Nagata et al teach that the codon optimization level of the genes correlate well with the translational efficiency in mammalian cells. This is concomitantly associated with the induction level of specific CTL response in the mouse using genes encoding major histocompatibility complex class I-restricted cytotoxic T-lymphocyte (CTL) epitopes, derived from an intracellular bacterium *Listeria monocytogenes* (see Table 1B and discussion). It is noted that the results of Nagata et al suggest that DNA immunization using the gene codon-optimized to mammals through the entire region is very effective (abstract). The teachings of Nagata et al suggest that the DNA sequence obtained by optimized codon usage of a host considerably increases both humoral and cellular immune responses (Figure 3 and discussion). Further, the teachings of Nagata et al indicate that synthetic human immunodeficiency virus type 1 gp120 sequence in which most wild-type codons were replaced with codons from highly expressed human genes (page 445, right column) is considerably increased in comparison to that of the respective wild-type sequence suggesting a direct correlation between expression levels of a protein obtained by codon optimization and the immune response. However, Nagata et al do not explicitly teach codon optimization for *B. anthracis*.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the nucleic acid composition described by Lee/Katritch/Collier and alter the bacterial codon usage to human codon usage as taught by Nagata et al and suggested by Lee et al to produce high yield of recombinant nucleic acid sequence encoding modified polypeptide for DNA vaccination. Nagata et al provided the

motivation to modify the nucleic acid sequence composition of because of its usage in vaccine development.

One who would practiced the invention would have had reasonable expectation of success because a composition comprising a polynucleotide disclosed by Lee/Katritch/Collier that is modified to alter the bacterial codon usage to human codon usage as taught by Nagata would help in preparing efficient DNA vaccine. An artisan of ordinary skills would have been motivated in using polynucleotide encoded by the sequence disclosed by Lee/Katritch/Collier et al and further optimize for human codon usage to obtain highly efficient DNA because the prior art suggests that codon optimized DNA preparation is effective (Nagata et al discussion and abstract). One of ordinary skill in art would have been motivated to combine the teaching of Lee/Katritch/Collier, and Nagata because a composition comprising codon optimized polynucleotide would have been excellent candidate for DNA vaccine against anthrax.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

14. No Claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla

can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Anoop Singh, Ph.D.
Examiner, AU 1632

Jon Weber
AU1632